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TITLE: **F18 EF5 PET/CT Imaging in Patients with Brain Metastases from Breast Cancer**

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14. ABSTRACT

The aim of this study is to estimate the degree of residual hypoxia after whole brain radiation therapy in patients with brain metastases from breast cancer as quantified by F18 EF5 PET/CT imaging. There has been great difficulty in accruing patient to this study due to the nature of the brain metastases resulting in cognitive decline, decline in performance status, and/or inability to complete the imaging study. We have amended the study to enhance accrual by opening to our satellite hospitals as well as those receiving stereotactic radiosurgery for brain metastases.

15. SUBJECT TERMS
18F EF5 PET/CT, breast cancer, brain metastases

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Introduction:

Brain metastases are a frequent neurologic complication of many solid tumors and have been reported to occur in approximately 5-15% of breast cancer patients. As a result of better systemic chemotherapeutic agents which have improved outcomes in breast cancer patients with metastatic disease, metastases in the central nervous system (CNS) have emerged as an important sanctuary site. Treatments to improve outcomes in patients with CNS disease is particularly important now as a growing proportion of patients may experience morbidity and/or mortality from CNS progression at a time when they have controlled extracranial disease. Whole brain radiotherapy is the standard treatment in patients with multiple brain metastases, however, 50% of patients may have local progression of one or more brain metastases at 6 months. Hypoxic and/or anoxic tissue may be a contributing factor to radiation resistance and high rates of local failure after standard radiotherapy. One method of overcoming radiation resistance is through the delivery of escalated doses of radiotherapy through stereotactic radiosurgery (RS), a non-invasive method of delivering highly conformal doses of radiotherapy in a single treatment, which has been demonstrated to improve local control and survival in select patients after WBRT. At present we do not have any method of determining *a priori* which patients may benefit from RS boost. The development of a noninvasive imaging biomarker to identify patients that are at highest risk of local relapse after WBRT would represent a significant step forward in the management of patients with brain metastases from breast cancer. We propose to use a noninvasive imaging method to detect residual tumor hypoxia in patients receiving WBRT.

Body:

Task 1. To estimate the degree of hypoxia after WBRT in patients with brain metastases from breast cancer as quantified by F18 EF5 PET/CT imaging.

Subtask 1a. Obtain IRB and DOD regulatory approval for prospective clinical trial entitled, “F18 EF5 PET/CT Imaging in patients with brain metastases from breast cancer” treated at the University of Pennsylvania Department of Radiation Oncology (months 1-3).

Protocol full approval was obtained from the University of Pennsylvania IRB on 09/23/11 and from U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) on 10/12/11. At that time, the temporary transfer of PI responsibility was granted to Dr. Gary Freedman, as the PI (Dr Lin) was going on maternity leave. An amendment was approved by the Penn’s IRB on 01/18/12 to return the PI responsibility back to Dr. Lilie Lin on her return from Leave of Absence. U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) approved this transfer on 02/12/12. Continuing Review of the protocol was approved by Penn’s IRB on 11/2/11 and the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP), Human Research Protection Office (HRPO) on 02/12/12.

Subtask 1b. Enroll and recruit patients for the clinical trial (months 3-21).

Accrual goal is 25 subjects; three subjects initially consented to the study. All three were unable to complete the imaging study at the required timepoint. This subject required a prospective protocol exception (deviation): after the subject was consented, it was found that she had very poor venous access and her imaging has been delayed until she can have a port placed. This exception was granted approval by the Penn IRB and by the Data Safety Monitoring Committee on 04/04/12. The Medical Monitor, Dr. Weijing Sun, was notified on 04/04/12 and did not raise objection to the exception. Unfortunately, she subsequently withdrew her consent for the study. The second patient developed progressive leptomeningeal disease and required spinal radiation leaving her fatigued and

unable to complete the study. A third patient did undergo the research brain MRI at the required timepoint, however, when she came in for her F18 EF5 PET/CT imaging, she was unable to lie supine for the duration of the scan due to her progressive pulmonary disease and pleural effusion. There have been no AEs or SAEs. A fourth patient was approached about the study and was interested, however, she developed progressive disease and has been placed on hospice.

The rate of accrual has been challenging with this protocol. At the time this protocol and grant was conceived, whole brain radiotherapy was more often recommended to patients with multiple brain metastases. We have had a change in the paradigm of treatment here at the University of Pennsylvania, where more patients are offered gamma knife radiotherapy upfront rather than whole brain radiotherapy which has impacted our accrual rates. Additionally, though we have had several patients that are interested in the study, many of them have concurrent extracranial disease. Patients with better performance status often receive upfront gamma knife radiotherapy instead which currently those patients are excluded from the study. To address these challenges, we modified the protocol to open the window of imaging to include during radiotherapy as well as up to four weeks post treatment. Additionally, opening up the protocol enrollment to include patients receiving gamma knife radiotherapy was done. Including patients with other types of primary malignancies has also been considered, however, was not approved by the scientific officer.

Two amendments were approved by the University of Pennsylvania IRB with the goal of increasing enrollment. The first amendment received approval on 01/14/2013 and expanded the targeted population to include patients whose treatment plan includes stereotactic surgery as well as those receiving whole brain radiation treatment. The second amendment received approval on 06/05/2013 and expanded the targeted population to include patients whose treatment plan includes sterotactic surgery as well as those receiving whole brain radiation treatment. Adding these subjects did not change the safety profile of the study or the expected risk to subjects.

Thirty-four patients were screened during this time. Seven patients were found to be eligible. Five of those patients declined as they were not interested in participating in the study. One patient died prior to initiation of therapy. One patient enrolled, however, she subsequently withdrew consent due to progressive disease

Key Research Accomplishments:

- IRB and CTSRMC (scientific review committee) approval of this prospective study at the University of Pennsylvania
- 3 patients were enrolled onto the study, however, were unable to complete the study as outlined for the reasons outlined above.
- Annual renewal of IRB and CTSRMC study.

Reportable outcomes

None to date

Conclusion:

Accrual goal is 25 subjects. Although several subjects were screened, no subjects were enrolled in this reporting period. Accrual continues to be our most pressing challenge with this protocol. We will continue to make amendments to the study to make it more feasible for patients to undergo imaging by

expanding the time period to make it increase flexibility.